

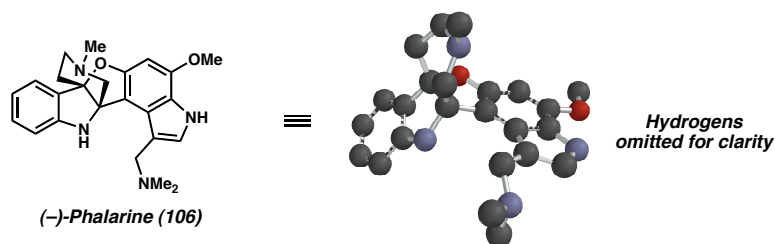
CHAPTER 3

Synthetic Efforts Toward (–)-Phalarine Using Palladium(II)-catalyzed Oxidative Heterocyclizations

3.1 Introduction and Biosynthesis

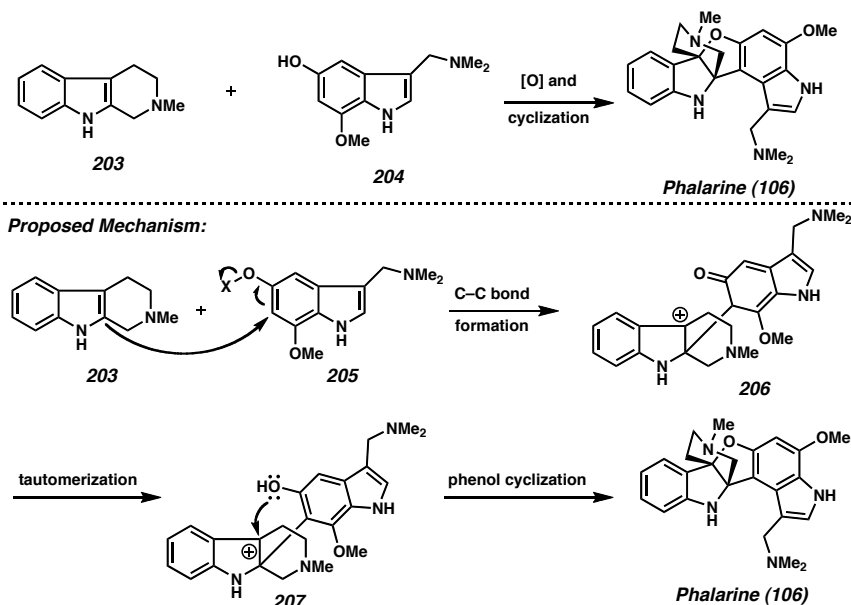
In 1999, (–)-phalarine (**106**) was isolated from *Phalaris coerulescens* and displayed a [4.3.3.0] fused tricyclic core structure including a novel furanobisindole ring system (Figure 3.1.1).^{1,2} In addition, the natural product contains vicinal stereocenters that are contained within the propellar-like core. Although (–)-phalarine (**106**) is not reported to be biologically active, the properties of this molecule still warrants medicinal evaluation since many alkaloids isolated from the genus *Phalaris* have proven to be poisonous to livestock when the native plant was ingested (e.g., canary grass, *P. arundinacea*).

Figure 3.1.1 (–)-Phalarine (**106**) in Two and Three Dimensions.



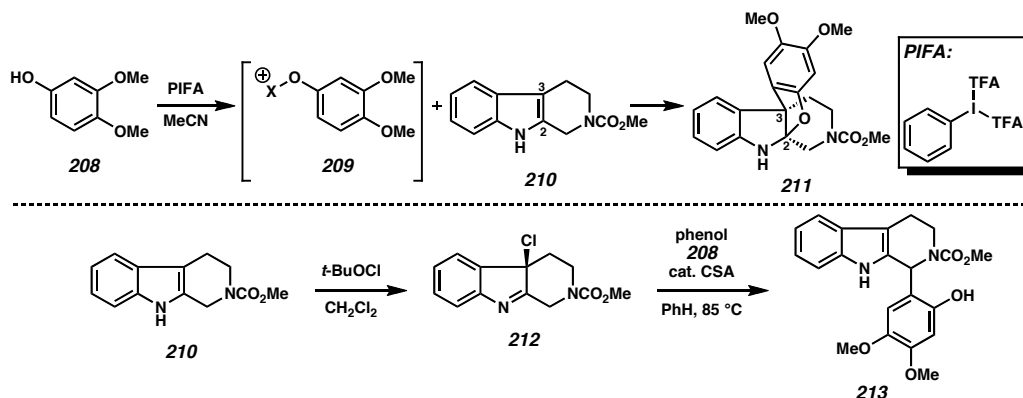
Although the biosynthesis of (–)-phalarine (**106**) has not been fully elucidated, it is proposed by the isolation chemists that (–)-phalarine (**106**) is obtained via an oxidative coupling of known tetrahydro- β -carboline **203** with a functionalized indole akin to phenol **204** (Scheme 3.1.1).³ It is hypothesized that indole **204** is oxidized to an intermediate similar to arene **205**. This activated intermediate undergoes addition by tetrahydro- β -carboline **203** to provide cationic species **206**, which will undergo rapid tautomerization to provide enol **207**. Formation of the natural product (**106**) is accomplished by the addition of the phenol in intermediate **207** onto the benzylic cation.

Scheme 3.1.1



Initial synthetic efforts by the Danishefsky laboratory to access the skeletal framework of the natural product using a biosynthetic approach proved unsuccessful. Their first attempt began with oxidation of phenol **208** to generate intermediate **209** (Scheme 3.1.2). Treatment of this intermediate with tetrahydro- β -carboline **210** provided polycycle **211** exclusively; however, the reaction occurred with undesired regioselectivity in the formation of the bridging dihydrobenzofuran functionality.⁴ A second generation approach employed oxidation of tetrahydro- β -carboline **210** with *t*-butyl hypochlorite to yield α -chloroimine **212**. Unfortunately, exposing imine **212** to phenol **208** in the presence of a catalytic amount of camphorsulfonic acid (CSA) in refluxing benzene afforded indole **213** as the sole product.⁵

Scheme 3.1.2



In the end, Danishefsky's efforts to synthesize the core of (–)-phalarine using a biomimetic strategy failed due to the lack of regio-control in the oxidative coupling step. These results infer that the proposed biosynthesis of (–)-phalarine (**106**) are likely catalyzed in a chiral environment that effects the key oxidative coupling reaction to provide the correct regiochemistry. Despite these synthetic challenges, Danishefsky's laboratory persisted, and in 2007 accomplished a total synthesis of racemic phalarine.

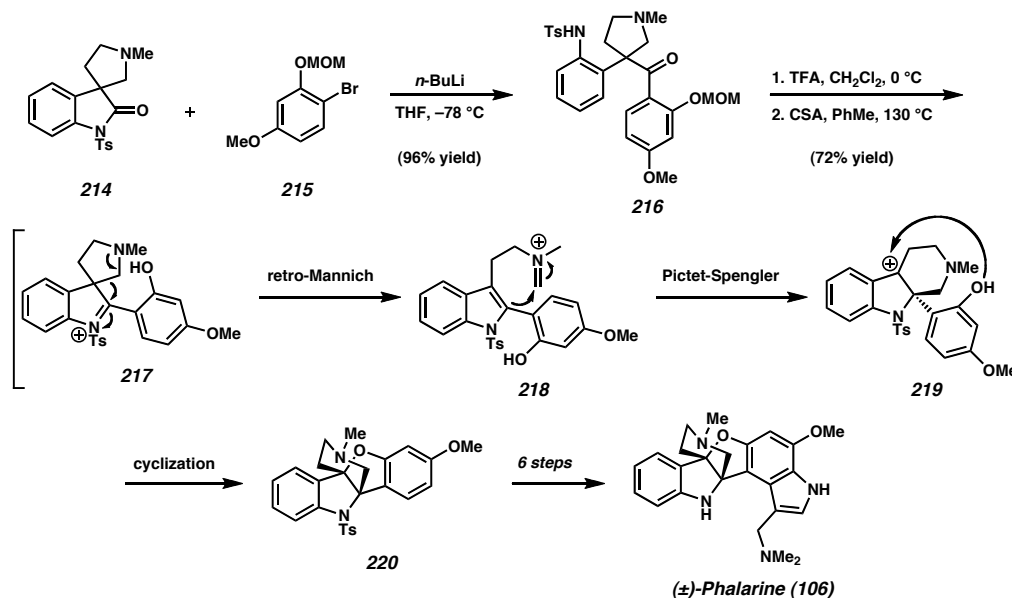
More recently, Danishefsky's laboratory completed an asymmetric synthesis of (–)-phalarine using a C(2)-functionalized tryptophan. The results of their work will be discussed in the next section.

3.2 Previous Efforts Toward the Total Synthesis of Phalarine

The only total syntheses of phalarine were reported by the Danishefsky laboratory in 2007 and 2010.⁶ The synthesis of racemic phalarine was accomplished using a key retro-Mannich reaction followed by a Pictet-Spengler cyclization to provide the core of the natural product (Scheme 3.2.1).

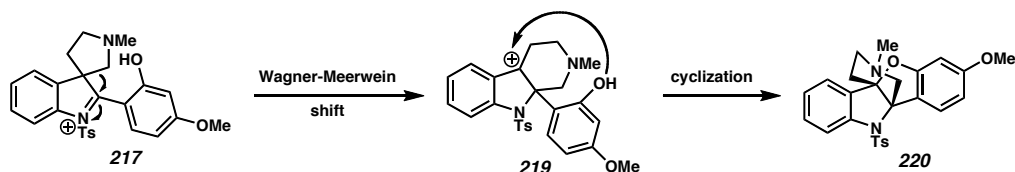
The key steps of the synthesis began with addition of lithiated arene **215** into oxindole **214** to provide ketone **216** in excellent yield. Exposing ketone **216** to two sequential organic acids first cleaved the MOM group, and then facilitated the condensation of the aniline onto the pendant ketone to provide iminium **217**. This activated species underwent a retro-Mannich reaction to generate intermediate **218**, which cyclized in a Pictet-Spengler fashion to form cationic intermediate **219**. Finally, cyclization of the phenol moiety furnished the core of phalarine (**220**) in 72% yield from ketone **216**.

Scheme 3.2.1



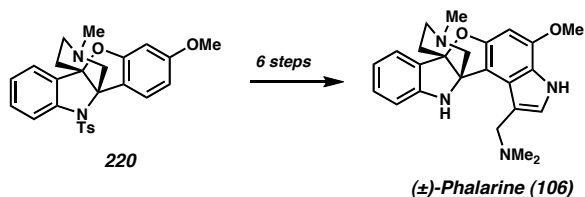
Although an alternate mechanism invoking a Wagner-Meerwein ring-expansion is plausible (Scheme 3.2.2), Danishefsky found that treatment of enantioenriched ketone **217** under the same conditions provided product **220** as a racemic mixture.⁷ This result indicates the formation of an achiral intermediate, such as iminium **218**, prior to product formation.

Scheme 3.2.2



With a rapid synthesis of pentacycle **220** complete, Danishefsky sought to complete the molecule by synthesizing the indole unit and appending the gramine side chain (Scheme 3.2.3).⁸ Although the synthesis of pentacycle **220** is rapid, the completion of phalarine required an additional six steps to synthesize the gramine moiety of the natural product.

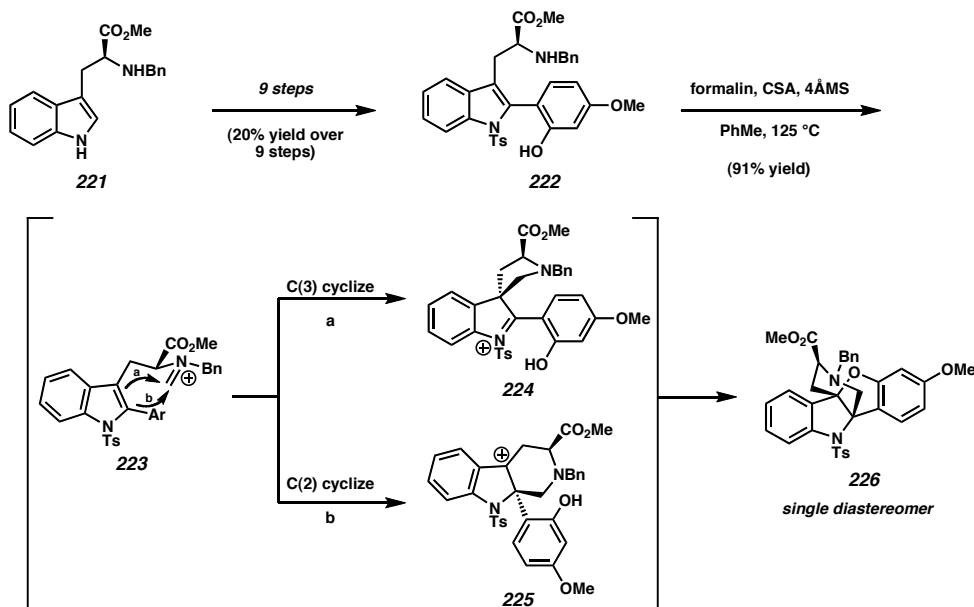
Scheme 3.2.3



Danishefsky's synthesis of racemic phalarine (**106**) required nine synthetic steps starting from oxindole **214**⁹ and provided the core of the natural product via a retro-Mannich reaction/Pictet-Spengler addition cascade sequence. Unfortunately, this reaction sequence occurred through an achiral intermediate, thus initially negating an asymmetric synthesis.

However, Danishefsky recently published an asymmetric synthesis of (–)-phalarine utilizing a chiral variant of iminium **218** (cf. Scheme 3.2.1). In an ingenious attempt, Danishefsky began with L-tryptophan methyl ester (**221**) to synthesize indole **222** in nine steps (Scheme 3.2.4). Exposing indole **222** to formalin under acidic conditions provided iminium **223**. This species underwent a Pictet-Spengler cyclization with either C(2) or C(3) of the indole moiety to provide intermediates **224** and **225**, respectively. Although it is unclear which mechanism is operative,¹⁰ the desired pentacycle (**226**) is obtained as a single diastereomer in 91% yield beginning from indole **222**. At this stage, an additional ten synthetic operations provided the desired natural product.

Scheme 3.2.4

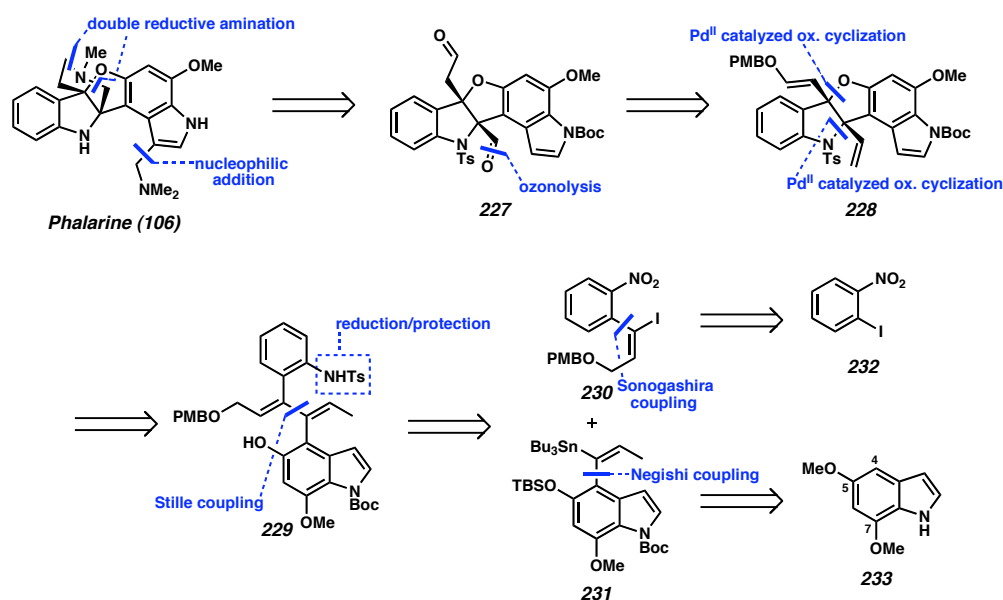


3.3 Retrosynthetic Analysis of Phalarine

Our retrosynthetic analysis of phalarine (**106**) began with late-stage formation of the bridging piperidine ring via a double reductive amination of bis-aldehyde **227** and methylamine (Scheme 3.3.1). We envisioned unveiling the two aldehyde units by an ozonolysis of a terminal olefin and hydrolysis of a PMB vinyl ether, which led us to intermediate **228**. We anticipated the formation of pentacycle **228** via a double palladium(II)-catalyzed oxidative heterocyclization beginning from diene **229**. At this stage, we planned to synthesize diene **229** from a Stille coupling between vinyl iodide **230** and vinyl stannane **231**. The synthesis of vinyl iodide **230** was seen to arise from known compound **232** by a Sonogashira coupling. However, we anticipated that the synthesis of vinyl stannane **231** would be difficult since fully differentiated 4,5,7-substituted indoles lack an efficient synthetic route that is compatible with many common

functional groups. Instead of addressing this problem prior to indole formation, we sought out indole **233** as a suitable starting point to effect differentiation between C(5) and C(7), and allow for selective C(4) functionalization.

Scheme 3.3.1

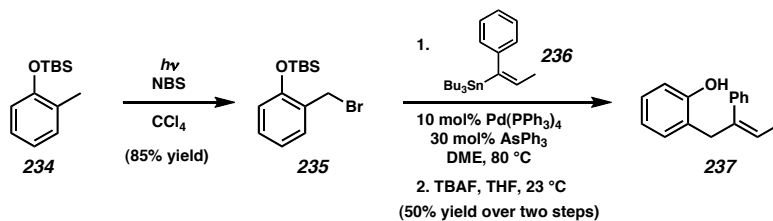


3.4 Model System Studies

There are very few examples of palladium(II)-catalyzed oxidative heterocyclizations onto styrenyl or conjugated olefins.¹¹ Thus, we decided to investigate the palladium(II)-catalyzed oxidative phenol cyclization using a model system.

We envisioned phenol **237** (Scheme 3.4.1) as a suitable substrate to test the palladium(II)-catalyzed oxidative cyclization since it possessed a trisubstituted styrenyl olefin that is similar to diene **229** (cf. Scheme 3.3.1). The synthesis of phenol **237** began with a radical bromination of arene **234** to provide benzyl bromide **235** in excellent yield.¹² From here, Stille coupling using known vinyl stannane **236** provided the desired product, which then underwent silyl cleavage to arrive at phenol **237** in 50% yield.¹³

Scheme 3.4.1



With the model substrate in hand, phenol **237** was subjected to the DMSO/O₂ conditions as well as conditions for the palladium(II)-catalyzed oxidative cyclization previously developed in our group.^{14,15} As shown in Table 3.4.1, using the DMSO/O₂ conditions without NaOAc allowed for an 80% yield of dihydrobenzofuran **238** in only 4 hours.¹⁶ Under our optimized conditions (Entry 3), the formation of dihydrobenzofuran **238** was significantly slower than the DMSO/O₂ conditions. Nevertheless, all entries in Table 3.4.1 provided dihydrobenzofuran **238** as the only observable product, with the remaining mass recovered as unreacted starting material.

Table 3.4.1 Attempts at the Pd(II)-catalyzed Oxidative Cyclization of Phenol **237**.

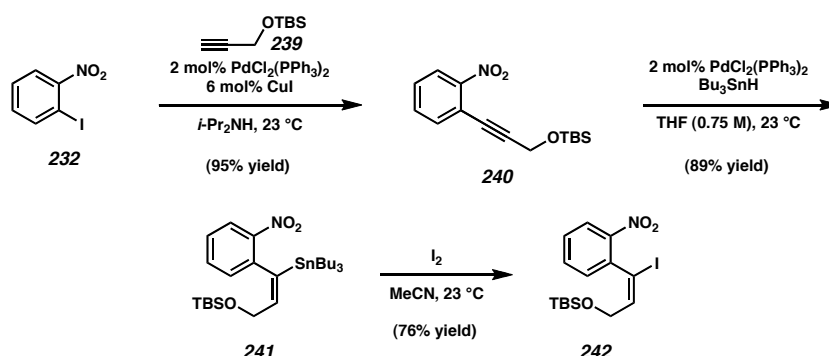
Entry	Conditions	Time (h)	Yield (%) ^a
1.	5 mol% Pd(TFA) ₂ 20 mol% pyridine	3	30
2.	3ÅMS, Na ₂ CO ₃ , O ₂ PhMe, 80 °C	18	60
3.	10 mol% Pd(OAc) ₂ 40 mol% pyridine 3ÅMS, O ₂ PhMe, 80 °C	2	25
4.	10 mol% Pd(OAc) ₂ , O ₂ DMSO, 60 °C	4	80
5.	5 mol% Pd(OAc) ₂ , NaOAc (2 equiv), O ₂ DMSO, 60 °C	3	20

^a Isolated yield.

3.5 Initial Synthetic Efforts

Our initial synthetic efforts focused on the synthesis of diene **229**, which could be used to test both the phenol and aniline palladium(II)-catalyzed oxidative heterocyclizations. Thus, beginning with 2-nitro iodobenzene (**232**), Sonogashira coupling of alkyne **239** provided arene **240** in high yield (Scheme 3.5.1). Regioselective hydrostannylation of alkyne **240** using conditions developed by Alami, provided vinyl stannane **241** in 65% yield.¹⁷ Subsequent exposure of this intermediate to I₂ in acetonitrile provided vinyl iodide **242** in 76% yield.¹⁸

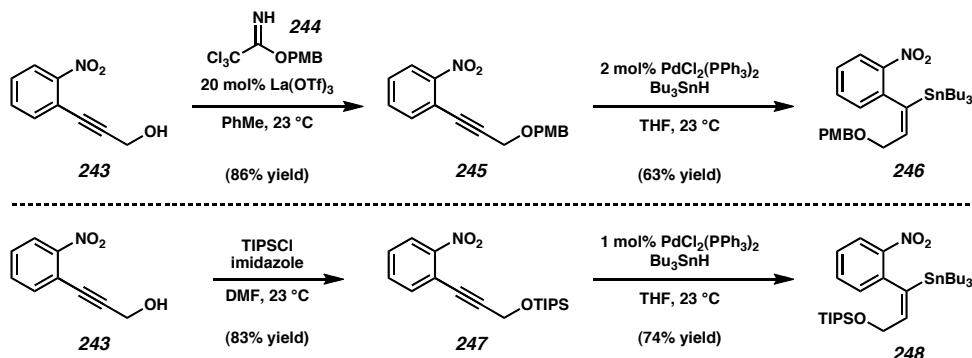
Scheme 3.5.1



Although we were confident that the TBS moiety in vinyl iodide **242** would be stable in upcoming transformations, we decided to synthesize vinyl stannanes **246** and **248**. We hypothesized that the TIPS group would provide greater bulk and stability, while the PMB moiety was an orthogonal functional group that would allow for a silyl protecting group on indole fragment **231** (Scheme 3.5.2). Accordingly, exposure of alcohol **243**¹⁹ to 20 mol% La(OTf)₃ and trichloroacetimidate **244**²⁰ provided alkyne **245** in 86% yield. Hydrostannylation of this product provided vinyl stannane **246** in 63% yield. The analogous TIPS protected intermediate was obtained via the aforementioned strategy. Silylation of alcohol **243** with TIPSCl proceeded in 83% yield, affording nitro-

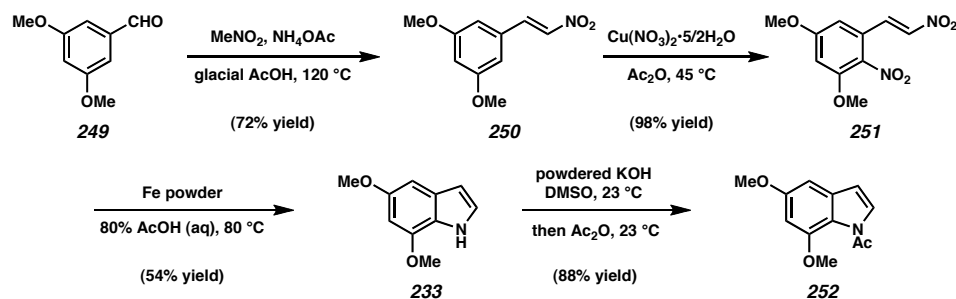
arene **247**. As expected, hydrostannylation of alkyne **247** proceeded regioselectively to furnish vinyl stannane **248** in 74% yield.

Scheme 3.5.2



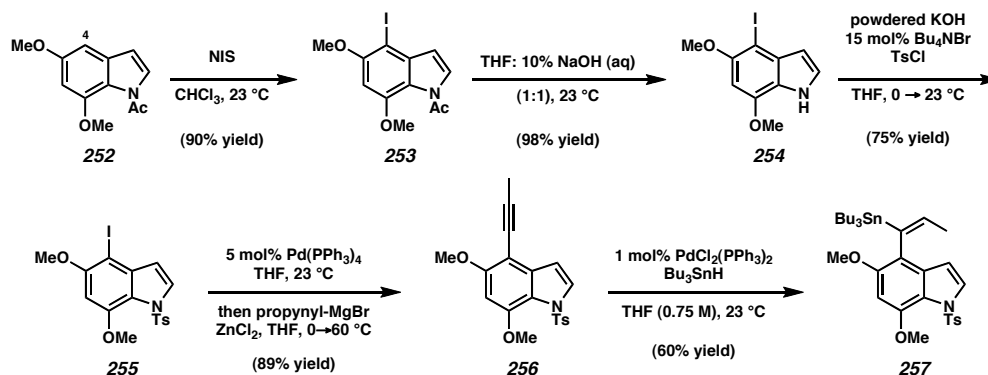
The second coupling partner needed for the Stille coupling, substituted indole **231**, was obtained from 5,7-dimethoxy indole (**233**).^{21,22} The synthesis of this indole is shown below in Scheme 3.5.3. Initial exposure of commercially available 3,5-dimethoxy benzaldehyde (**249**) to nitromethane under acidic conditions effected a Henry reaction to provide arene **250** in 72% yield.²³ Subsequent nitration using copper(II)nitrate in acetic anhydride provided nitro-arene **251** in 98% yield. At this stage, reductive cyclization afforded indole **233**, which underwent protection of the indole nitrogen as an amide, providing *N*-acyl indole **252** in 88% yield.

Scheme 3.5.3



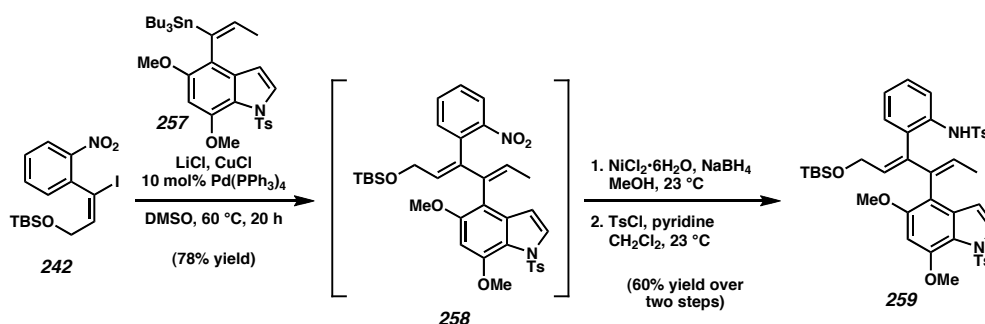
With the synthesis of indole **252** complete, we attempted to demethylate the two methoxy substituents on the indole core. Dimethoxy indole **252** proved surprisingly difficult to demethylate and all attempts were unsuccessful.²⁴ Hence, we elected to use this dimethylated system to probe the feasibility of the palladium(II)-catalyzed oxidative aniline cyclization. To this end, we needed to first functionalize, and then transform, C(4) of indole **252** to the appropriate vinyl stannane for the Stille coupling. Black has shown that formylation of 5,7-dimethoxyindoles occurs exclusively at C(4), rather than at C(3), when an acyl group (e.g., Ac, Piv, or Boc) is protecting the indole nitrogen.²⁵ Hence, selective C(4) functionalization commenced with iodination of indole **252** using NIS to provide intermediate **253** in excellent yield (Scheme 3.5.4). At this stage, it was found that the acetyl moiety was not stable toward further functionalization at C(4) via a Negishi coupling. To address this chemoselectivity issue, we sought a more robust protecting group. Thus, cleavage of the acyl amide provided indole **254** in nearly quantitative yield. Reprotection of the indole nitrogen in arene **254** as a sulfonamide afforded indole **255** in 75% yield. Further elaboration at C(4) occurred smoothly via a Negishi coupling providing alkyne **256** in excellent yield. Completion of the Stille coupling partner (**257**) was accomplished in 65% yield using a regioselective palladium-catalyzed hydrostannylation reaction.¹⁰

Scheme 3.5.4



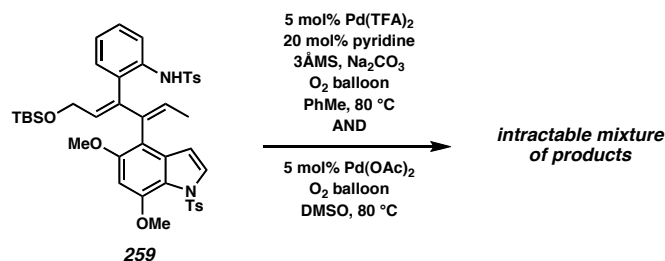
With both Stille coupling fragments in hand, we attempted the carbon-carbon bond-forming reaction. In the event, coupling of arene **242** with indole **257** provided intermediate **258** in good yield using conditions developed by Han, Stoltz, and Corey (Scheme 3.5.5).²⁶ At this stage, reduction of the nitro functionality was accomplished under pH-neutral conditions, followed by formation of a sulfonamide to afford diene **259** in 55% yield over the two steps.²⁷

Scheme 3.5.5



We then subjected tosyl aniline **259** to our conditions developed for the palladium(II)-catalyzed oxidative cyclization conditions (Scheme 3.5.6). Unfortunately, these conditions afforded an intractable mixture of products. We also tried DMSO/O_2 , although the same mixture of products was formed.²⁸

Scheme 3.5.6



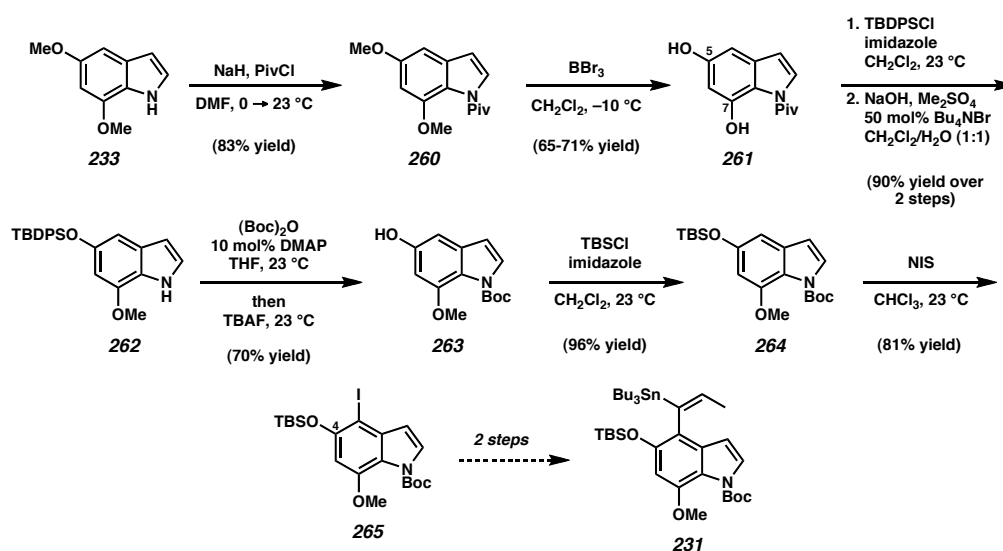
Since our phenolic model system was successful, we reconcentrated our efforts toward accessing the C(5) phenol contained on the indole fragment.

3.6 Further Studies Toward the Pd(II)-catalyzed Oxidative Phenol Cyclization

As previously stated, attempts to demethylate *N*-acetyl 5,7-dimethoxyindole (**252**, cf. Scheme 3.5.3) were unsuccessful. We speculated that the acetyl unit was cleaved when demethylation was attempted using BBr₃. Thus, we replaced the acetyl moiety with a pivaloyl group to provide greater stability and steric bulk, as well as to preserve exclusive functionalization at C(4) (Scheme 3.6.1). Beginning with 5,7-dimethoxyindole (**233**), protection of the indole nitrogen using pivaloyl chloride provided arene **260** in 83% yield. To our delight, demethylation of indole **260** occurred smoothly at –10 °C using BBr₃ to provide bis-phenol **261** in good yield.²⁹ At this stage, selective silylation of the C(5) phenol using TBDPSCl under standard conditions, followed by methylation at C(7) and pivaloate removal led to indole **262** in 90% overall yield. Further functionalization of indole **262** was accomplished by a two-step sequence beginning with Boc protection of the indole nitrogen, followed by silyl cleavage to arrive at phenol **263** in 70% overall yield. It was found that the TBDPS group prevented iodination at C(4) of

the indole, likely because of steric hindrance, and thus, was replaced with a TBS group. With phenol **263** in hand, protection as a TBS silyl ether occurred readily to yield arene **264**. Subsequent iodination using NIS provided indole **265** in 80% yield. By accessing indole **265**, we have accomplished our goal of synthesizing a differentially substituted 4,5,7-substituted indole from indole **233**. Furthermore, indole **265** should provide vinyl stannane **231** in two additional synthetic transformations.

Scheme 3.6.1



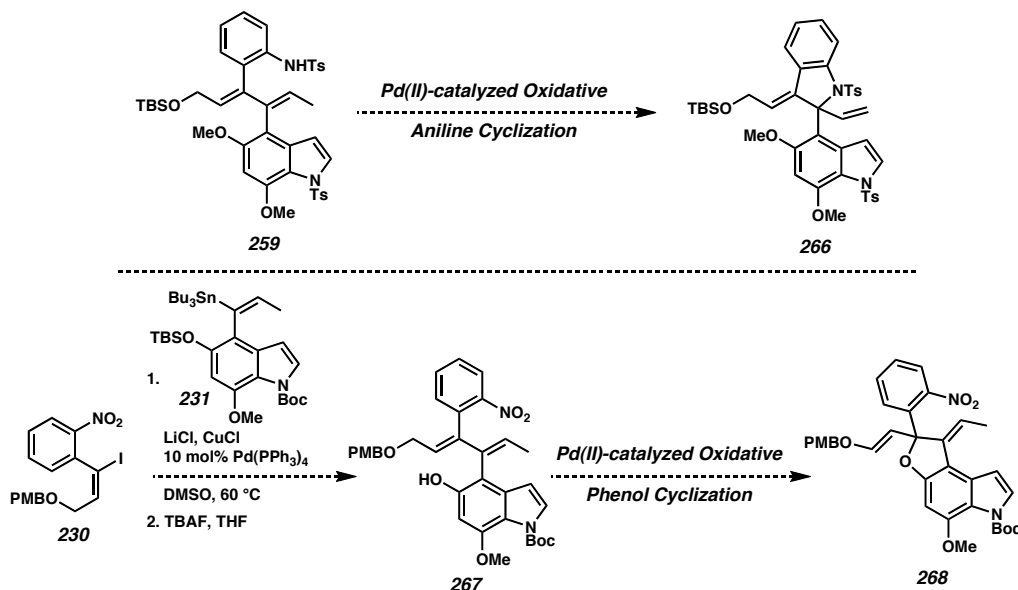
Although we are now able to access the C(5) phenol, further functionalization at C(4) is required to reach vinyl stannane **231**, which is needed for a Stille coupling and subsequent palladium(II)-catalyzed oxidative phenol cyclization. Thus, optimization of our protecting group strategy, as well as the synthesis of vinyl stannane **231** must occur to continue the synthesis.

3.7 Conclusions and Future Directions

The efforts described in this chapter have established an efficient synthesis to advanced intermediates that can be further functionalized and modified en route to phalarine. In general, the synthesis of 4,5,7 differentially substituted indoles can be difficult; nevertheless, we have developed an efficient route that allows for selective functionalization at each position, and thus allows for the possibility of accessing novel indoles that may be bioactive or found in nature.

The key aspects of the proposed synthesis of phalarine involved two palladium(II)-catalyzed oxidative heterocyclizations. Due to the efforts in this chapter, the aniline cyclization can be tested immediately. Furthermore, the synthesis of phenol **267**, needed for testing the other palladium(II)-catalyzed oxidative cyclization, is only several synthetic operations away from being synthesized (Scheme 3.7.1).

Scheme 3.7.1



Once results from the two palladium(II)-catalyzed oxidative heterocyclizations, shown in Scheme 3.7.1, have been obtained, it should become evident as to how to complete the synthesis of phalarine.

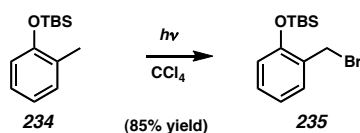
3.8 Experimental Procedures

3.8.1 Materials and Methods

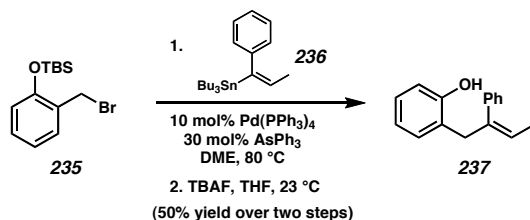
Unless otherwise stated, reactions were performed at ambient temperature (typically 20–22 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry solvents. Solvents were dried by passage through an activated alumina column under argon. Et₃N, *i*Pr₂NH, *i*Pr₂NEt, and pyridine were freshly distilled from CaH₂. Trifluoroacetic acid (99%) was purchased from Aldrich. Tf₂O was freshly distilled from P₂O₅. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, KMnO₄, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz respectively) and are reported relative to solvent for ¹H NMR (CHCl₃ = 7.27 ppm, C₆H₆ = 7.16 ppm, CH₂Cl₂ = 5.30 ppm, DMSO = 2.51 ppm) and ¹³C NMR (CDCl₃ = 77.0 ppm, C₆D₆ = 128.4 ppm). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, hex = hextet, dq = doublet of quartets, dt = doublet of triplets, td = triplet of doublets, dd = doublet of doublets, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer BX-11 FT-IR spectrometer and are reported in

frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. For reactions involving UV light, a Mercury UV-lamp was used.

3.8.2 Preparation of Compounds



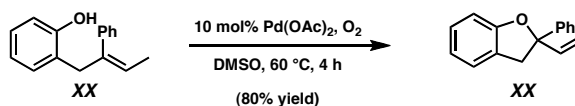
Benzyl Bromide 235. To a solution of arene **234**¹² (1.00 g, 4.50 mmol, 1.00 equiv) in CCl_4 (40 mL) at ambient temperature was added NBS (881 mg, 4.95 mmol, 1.10 equiv). A reflux condenser was fitted onto the reaction (no water) as a precaution. The reaction mixture was then stirred for 2 hours with continuous irradiation using UV light. At this time, TLC (100% Hexanes) showed the reaction was complete. The reaction mixture was filtered with filter paper, washed with minimal CH_2Cl_2 , and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography using 100% Hexanes to provide a clear oil (1.15 g, 85%). All spectroscopic data of benzyl bromide **235** matched those reported by Hartwig.¹²



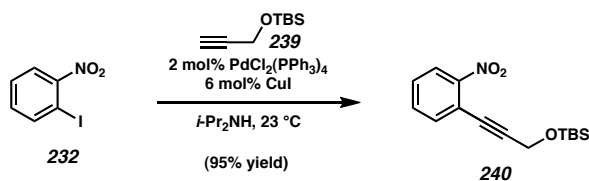
Phenol 237. A round-bottom flask was charged with benzyl bromide **235** (510 mg, 1.69 mmol, 1.00 equiv) and vinyl stannane **236**¹³ (825 mg, 2.03 mmol, 1.20 equiv), followed

by DME (17 mL). This solution was sparged for 10 minutes with argon, followed by the sequential addition of AsPh_3 (155 mg, 0.507 mmol, 0.300 equiv) and $\text{Pd(PPh}_3)_4$ (195 mg, 0.169 mmol, 0.100 equiv) at ambient temperature, and fitted with a reflux condenser (no water). The reaction mixture was heated to 80 °C, and monitored by TLC (100% Hexanes). After 6–8 hours, the reaction was complete and diluted with Et_2O to provide a white precipitate. This suspension was filtered through a small pad of celite, and the Et_2O layer was washed with water and brine, dried with MgSO_4 , filtered, and concentrated in vacuo to provide a crude oil.

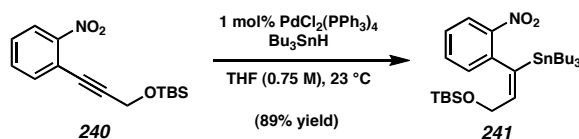
To this oil was added THF (17 mL) at ambient temperature, followed by TBAF (2.03 mL of 1.0 M solution in THF, 2.03 mmol, 1.20 equiv). After 1 hour, TLC (10:90 EtOAc:Hexanes) showed the reaction was complete. The reaction was diluted with Et_2O and water, and the layers were separated. The aqueous layer was extracted 2x with Et_2O , and the Et_2O layers were combined and washed with water and brine, dried with MgSO_4 , filtered, and concentrated in vacuo to provide an oil. This crude oil was purified by flash chromatography using 7:93 EtOAc:Hexanes to provide phenol **237** as a clear oil (189 mg, 50% yield over two steps). R_F = 0.40 (15:85 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.32 (t, J = 7.3 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.14 (m, 3H), 7.02 (d, J = 6.8 Hz, 1H), 6.82 (t, J = 8.3 Hz, 2H), 5.64 (q, J = 6.8 Hz, 1H), 5.04 (s, 1H), 3.68 (s, 2H), 1.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 154.5, 140.2, 139.8, 131.1, 128.3, 128.2, 127.9, 126.8, 124.9, 123.4, 120.8, 115.9, 40.5, 14.7; IR (film) 3468, 3030, 2914, 1592, 1489, 1455, 1215 cm^{-1} ; HRMS (FAB^+) calc'd for $[\text{C}_{16}\text{H}_{16}\text{O}]^+$: m/z 224.1201, found 224.1206.



Dihydrobenzofuran 238. To a 14/20 fitted glass tube (6.00 mL capacity) containing phenol **237** (10.0 mg, 44.6 μmol , 1.00 equiv) was added $\text{Pd}(\text{OAc})_2$ (1.00 mg, 4.46 μmol , 0.100 equiv) followed immediately by DMSO (890 μL) at ambient temperature. A 14/20 fitted glass three-way adapter containing an O_2 balloon was attached accordingly. The reaction mixture was purged under vacuum and backfilled with O_2 , and repeated 4x. The reaction mixture was then heated to 60 $^\circ\text{C}$ and monitored by TLC (20:80 EtOAc:Hexanes). After 4 hours the reaction was complete. The reaction mixture was allowed to cool to ambient temperature, and the dark solution was transferred to a biphasic system of Et_2O :brine (2:1). The layers were separated, and the aqueous layer was extracted 3x with Et_2O . The Et_2O layers were combined and washed with brine, dried with MgSO_4 , filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide dihydrobenzofuran **238** as a colorless oil (8.00 mg, 80%). $R_F = 0.35$ (30:70 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, $J = 7.3$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.28 (app. d, $J = 7.3$ Hz, 1H), 7.16 (m, 2H), 6.94 (d, $J = 7.8$ Hz, 1H), 6.86 (t, $J = 7.6$ Hz, 1H), 6.23 (dd, $J = 10.5, 17.1$ Hz, 1H), 5.30 (dd, $J = 0.9, 17.1$ Hz, 1H), 5.18 (dd, $J = 0.9, 10.5$ Hz, 1H), 3.60 (d, $J = 15.4$ Hz, 1H), 3.56 (d, $J = 15.4$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.7, 144.0, 141.0, 128.3, 128.2, 127.3, 125.9, 125.4, 124.9, 120.7, 114.0, 109.5, 90.7, 42.8; IR (film) 3056, 3031, 1598, 1480, 1462, 1241; HRMS (FAB $^+$) calc'd for $[\text{C}_{16}\text{H}_{14}\text{O}]^+$: m/z 222.1045, found 222.1035.

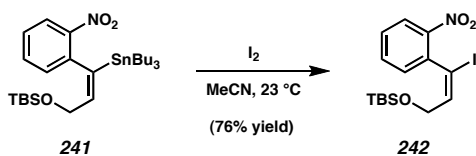


Alkyne 240. To a solution of arene **232** (2.50 g, 10.0 mmol, 1.00 equiv) and alkyne **239** (5.11 g, 30.0 mmol, 3.00 equiv) in *N,N*-diisopropylamine (33 mL) at ambient temperature, $\text{PdCl}_2(\text{PPh}_3)_2$ (140 mg, 0.200 mmol, 0.0200 equiv) and CuI (115 mg, 0.600 mmol, 0.0600 equiv) were added sequentially to the reaction. A slurry formed after several minutes, and the reaction mixture was monitored by TLC (20:80 EtOAc:Hexanes). After 30–60 minutes, the reaction was complete, and diluted with saturated NaHCO_3 (aq.). The aqueous layer was extracted 3x with Et_2O , and the Et_2O layer was then washed 2x with water, once with brine, dried with MgSO_4 , filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to provide alkyne **240** as an oil (2.77 g, 95% yield). All spectroscopic data were identical to those reported by Sakamoto.³⁰



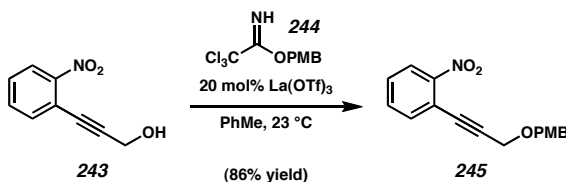
Vinyl Stannane 241. To a solution of alkyne **240** (1.00 g, 3.43 mmol, 1.00 equiv) and $\text{PdCl}_2(\text{PPh}_3)_2$ (24.0 mg, 0.0343 mmol, 0.0100 equiv) in THF (4.60 mL) at ambient temperature was added Bu_3SnH (1.10 mL, 4.12 mmol, 1.20 equiv) over 30 seconds, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). After 3 hours, the reaction was complete and was concentrated in vacuo to provide a dark oil that was purified by flash chromatography using 1:99 EtOAc:Hexanes to provide vinyl stannane **241** as a

yellow oil (1.78 g, 89% yield). R_F = 0.35 (5:95 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.04 (d, J = 8.3 Hz, 1H), 7.54 (dt, J = 0.7, 7.5 Hz, 1H), 7.33 (dt, J = 1.0, 7.3 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 5.94 (t, J = 5.6 Hz, 1H), 4.02 (t, J = 5.8 Hz, 2H), 1.44 (m, 6H), 1.30 (hex, J = 7.3 Hz, 6H), 0.97–0.84 (m, 24H), 0.020 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.0, 143.7, 141.0, 139.9, 133.0, 129.2, 126.0, 124.5, 61.7, 28.8, 27.3, 25.8, 18.2, 13.6, 10.6, –5.2, –5.3; IR (film) 2957, 2929, 2856, 1523, 1464, 1343, 1254, 1102 cm^{-1} ; HRMS (FAB $^+$) calc'd for $[\text{C}_{27}\text{H}_{48}\text{SiSnO}_3\text{N}]^+$: m/z 582.2426, found 582.2451.

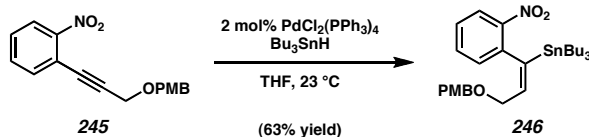


Vinyl Iodide 242. To a solution vinyl stannane **241** (1.10 g, 1.89 mmol, 1.00 equiv) in MeCN (19.0 mL) at ambient temperature was added I_2 (528 mg, 2.08 mmol, 1.10 equiv) in several portions, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). After 1 hour, the reaction was complete, and was quenched with 5% $\text{Na}_2\text{S}_2\text{O}_3$ (aq.). The reaction mixture was diluted with water and Et_2O , and the layers were then separated. The Et_2O layer was washed with water and brine, dried with MgSO_4 , filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 2:98→5:95 EtOAc:Hexanes to provide vinyl iodide **242** as a pale-yellow oil (600 mg, 76% yield) R_F = 0.40 (10:90 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.00 (dd, J = 1.1, 8.2 Hz, 1H), 7.62 (dt, J = 1.2, 7.5 Hz, 1H), 7.48 (dt, J = 1.5, 8.2 Hz, 1H), 7.38 (dd, J = 1.2, 7.6 Hz, 1H), 6.63 (t, J = 6.5 Hz, 1H), 3.88 (dq, J = 6.5, 13.2 Hz, 2H), 0.82 (s, 9H), –0.060 (s, 3H), –0.072 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.0, 143.2, 136.3,

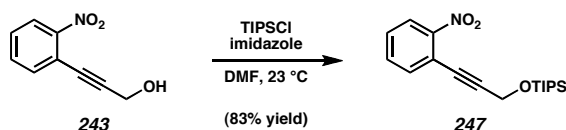
133.3, 130.7, 129.4, 124.7, 88.5, 61.9, 25.8, 18.2, –5.4, –5.5; IR (film) 2954, 2929, 2857, 1529, 1472, 1348, 1257, 1103 cm^{-1} ; HRMS (FAB⁺) calc'd for $[\text{C}_{15}\text{H}_{23}\text{O}_3\text{N}\text{Si}]^+$: m/z 470.0492, found 420.0480.



Alkyne 245. To a solution of alcohol **243** (448 mg, 2.53 mmol, 1.00 equiv) and reagent **244**^{20a} (1.00 g, 3.54 mmol, 1.40 equiv) in PhMe (12.7 mL) at ambient temperature was added La(OTf)₃ (296 mg, 0.506 mmol, 0.200 equiv), and the reaction was monitored by TLC (20:80 EtOAc:Hexanes). After 24 hours the reaction was complete by TLC, and quenched with water. The reaction mixture was diluted with Et₂O, and the layers are separated. The organic extract was washed with water and brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide a crude oil that was purified by flash chromatography using 15:85 EtOAc:Hexanes to obtain alkyne **245** as a red-orange semi-solid (650 mg, 86% yield). R_F = 0.40 (30:70 EtOAc:Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, J = 7.8 Hz, 1H), 7.65 (dd, J = 1.0, 7.8 Hz, 1H), 7.59 (dt, J = 1.0, 7.8 Hz, 1H), 7.48 (dt, J = 1.5, 7.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.67 (s, 2H), 4.44 (s, 2H), 3.82 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 159.5, 149.8, 134.9, 132.8, 130.0, 129.3, 128.8, 124.6, 118.1, 113.9, 93.6, 81.6, 71.3, 57.3, 55.3; IR (film) 2838, 1610, 1525, 1514, 1343, 1248, 1073, 1034 cm^{-1} ; HRMS (FAB⁺) calc'd for $[\text{C}_{17}\text{H}_{15}\text{O}_4\text{N}]^+$: m/z 297.1001, found 297.1007.

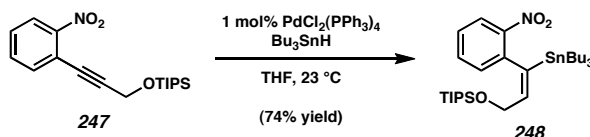


Vinyl Stannane 246. To a solution of alkyne **245** (605 mg, 2.03 mmol, 1.00 equiv) and $\text{PdCl}_2(\text{PPh}_3)_2$ (28.5 mg, 0.0406 mmol, 0.0200 equiv) in THF (2.70 mL) at ambient temperature was added Bu_3SnH (655 μL , 2.44 mmol, 1.20 equiv) over 60 seconds. The reaction was monitored by TLC (20:80 EtOAc:Hexanes), and was complete after 30 minutes. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography using 6:94 EtOAc:Hexanes to provide vinyl stannane **246** as a neon oil (755 mg, 63% yield). $R_f = 0.35$ (20:80 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, $J = 8.3$ Hz, 1H), 7.48 (dt, $J = 1.0, 7.8$ Hz, 1H), 7.28 (dt, $J = 1.5, 8.3$ Hz, 1H), 7.18 (d, $J = 8.3$ Hz, 2H), 7.04 (dd, $J = 1.0, 7.8$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 2H), 5.96 (t, $J = 5.9$ Hz, 1H), 4.32 (d, $J = 11.2$ Hz, 1H), 4.30 (d, $J = 11.2$ Hz, 1H), 3.80 (comp. m, 5H), 1.44 (hex, $J = 7.3$ Hz, 6H), 1.26 (hex., $J = 7.3$ Hz, 6H), 0.88 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.1, 147.2, 145.9, 140.9, 136.7, 133.0, 130.3, 129.3, 129.1, 126.1, 124.5, 113.7, 71.8, 67.9, 55.2, 28.8, 27.3, 13.6, 10.7; IR (film) 2956, 2927, 2853, 1613, 1517, 1464, 1342, 1285, 1080, 1038 cm^{-1} ; HRMS (FAB $^+$) calc'd for $[\text{C}_{25}\text{H}_{34}\text{SnO}_4\text{N}]^+$ (–Bu group): m/z 532.1510, found 532.1524.



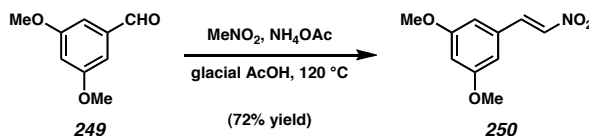
Alkyne 247. To a solution of alcohol **243** (2.49 g, 14.1 mmol, 1.00 equiv) and imidazole (2.01g, 29.6 mmol, 2.10 equiv) in DMF (56.0 mL) at 0 $^\circ\text{C}$ was added TIPSCl (3.04 mL, 14.8 mmol, 1.05 equiv). The reaction mixture was allowed to warm to ambient

temperature and stir overnight. TLC analysis (30:70 EtOAc:Hexanes) revealed the reaction was complete. The reaction mixture was diluted with water and Et₂O, and the layers were separated. The aqueous layer was extracted 3x with Et₂O, the Et₂O layers were combined, washed 3x with water, once with brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to provide alkyne **247** as a light-yellow oil (3.92 g, 83% yield). *R*_F = 0.30 (10:90 EtOAc:Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.10 (dd, *J* = 1.2, 8.3 Hz, 1H), 7.63 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.54 (dt, *J* = 1.2, 7.8 Hz, 1H), 4.69 (s, 2H), 1.20 (comp. m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 149.4, 134.9, 132.7, 128.6, 124.5, 118.4, 96.2, 79.6, 52.6, 17.9, 12.0; IR (film) 2944, 2866, 1609, 1569, 1530, 1463, 1344, 1261, 1098 cm⁻¹; HRMS (FAB⁺) calc'd for [C₁₈H₂₈NSiO₃]⁺: *m/z* 334.1838, found 334.1843.

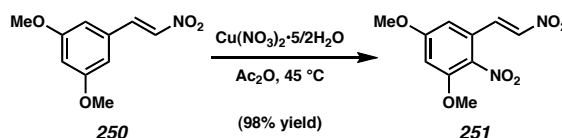


Vinyl Stannane 248. To a solution of alkyne **247** (3.90 g, 11.7 mmol, 1.00 equiv) and PdCl₂(PPh₃)₂ (82.1 mg, 0.117 mmol, 0.0100 equiv) in THF (16.0 mL) at ambient temperature was added Bu₃SnH (3.47 mL, 12.9 mmol, 1.10 equiv) over 30–45 seconds. The reaction darkens, and was monitored by TLC (5:95 EtOAc:Hexanes). After stirring overnight, the reaction mixture was concentrated in vacuo to provide a crude oil that was purified by flash chromatography using 2:98 EtOAc:Hexanes to provide vinyl stannane **248** as a neon-yellow liquid (5.44 g, 74% yield). *R*_F = 0.40 (5:95 EtOAc:Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.0 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.50 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.28 (dt, *J* = 1.5, 8.3 Hz, 1H), 7.08 (dd, *J* = 1.5, 7.8 Hz, 1H), 5.93 (t, *J* = 5.5 Hz, 1H), 4.02

(m, 2H), 1.44 (hex, $J = 7.1$ Hz, 6H), 1.25 (hex, $J = 7.3$ Hz, 6H), 1.00 (s, 18H), 0.86 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.1, 143.2, 141.0, 140.3, 133.0, 129.2, 126.0, 124.5, 61.9, 28.8, 27.3, 17.9, 13.6, 12.0, 10.7; IR (film) 2957, 2867, 1524, 1464, 1342, 1105, 1064 cm^{-1} ; HRMS (FAB $^+$) calc'd for $[\text{C}_{26}\text{H}_{46}\text{O}_3\text{NSnSi}]^+$: m/z 568.2269, found 568.2268.

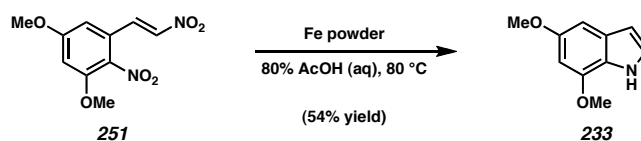


Arene 250. 3,5-dimethoxybenzaldehyde (**249**) (50.0g, 0.301 mol, 1.00 equiv), nitromethane (50.1 mL, 0.923 mol, 3.07 equiv), and ammonium acetate (76.0 g, 0.998 mol, 1.07 equiv) were dissolved in glacial acetic acid (615 mL) and refluxed for 2 h. The reaction mixture was allowed to cool to ambient temperature, at which time yellow crystals form. The suspension was placed in an ice bath for 30 minutes, and the product was then filtered and washed with cold 95% ethanol to provide compound **250** as yellow needles (45.3 g, 72% yield). All spectroscopic data of arene **250** matched those reported by Black.¹²



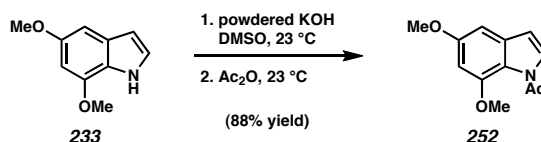
Arene 251. To a flask containing acetic anhydride (380 mL) warmed to 65°C was added compound **250** (40.0 g, 0.191 mol, 1.00 equiv). This suspension was stirred at 65°C until all of compound **250** had dissolved. Once homogeneous, the solution was allowed to cool to 45°C , and $\text{Cu}(\text{NO}_3)_2 \cdot 5/2\text{H}_2\text{O}$ (30.9 g, 0.105 mol, 0.550 equiv) was added in

4–5 portions over 1–2 minutes. A slight exotherm occurs, and once brown fumes appeared (ca. 5 min), the reaction was complete and allowed to cool to ambient temperature. The reaction mixture was poured over ice and allowed to stir and warm to ambient temperature overnight. The resulting yellow solid was filtered and washed with water 3x to provide arene **251** (47.6 g, 98% yield). All spectroscopic data of arene **251** matched those reported by Black.¹²

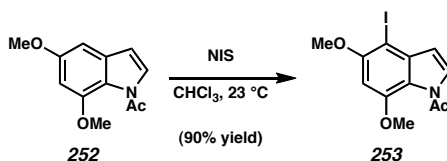


Indole 233. Iron powder (32.0 g, 576 mmol, 38.5 equiv) was added to a solution of arene **251** (4.00 g, 15.7 mmol, 1 equiv) in 80% acetic acid (130 mL) and the suspension was stirred mechanically. After an exotherm that lasts approximately 30 minutes, 40 mL of water was added and the suspension was heated to 80 °C for 1 hour. The reaction mixture was then allowed to cool to ambient temperature. Upon cooling, the reaction mixture hardens to become a single solid. This solid was partially dissolved by adding CH₂Cl₂ and 10% HCl (aq.), followed by manual irritation using a sturdy spatula until stirring with a mechanical stirrer became possible. This suspension stirred for an additional hour, and was then filtered over a large pad of celite. The solids were washed 6x with CH₂Cl₂, and the resulting biphasic solution was separated respectively. The CH₂Cl₂ layer was washed 3x with water, followed by slow addition of saturated cold Na₂CO₃ (aq.) until the organic layer was only slightly acidic (pH = 5–6). The organic layer was then washed with brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide a black solid. This residue was dissolved in minimal CH₂Cl₂, and purified by

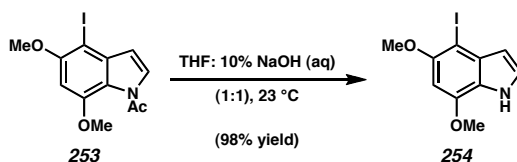
flash chromatography using 10:90 EtOAc:Hexanes to provide indole **233** as a white crystalline solid (1.50 g, 54% yield).³¹ All spectroscopic data of arene **233** matched those reported by Black.¹²



Indole 252. To powdered KOH (0.95 g, 16.9 mmol, 3.70 equiv) was added DMSO (20.0 mL) and the suspension was stirred at ambient temperature for 10 min. Indole **233** (0.800 g, 4.52 mmol, 1.00 equiv) was then added in one portion, and the suspension was allowed to stir for 1 hour. At this stage, the resulting solution was rapidly decanted from the excess KOH and transferred to a separate round-bottom flask containing chilled Ac₂O (4.00 mL, excess) (ice-bath). The excess KOH was washed rapidly with DMSO (5.00 mL) and quickly transferred to the solution of Ac₂O. This solution was allowed to warm to ambient temperature, and stirred under N₂ overnight. The reaction mixture was diluted with water and extracted 3x with Et₂O. The organic layer was washed with water and brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 10:90 EtOAc:Hexanes to provide indole **252** as a beige solid (867 g, 88% yield). All spectroscopic data of arene **252** matched those reported by Black.¹²

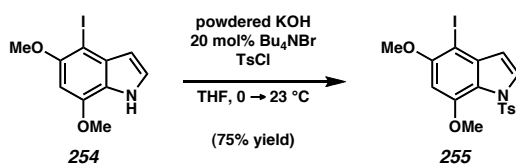


Arene 253. To a solution of indole **252** (4.62 g, 21.1 mmol, 1.00 equiv) in CHCl_3 (85.0 mL) at 0 °C, was added *N*-iodosuccinimide (5.22 g, 23.2 mmol, 1.10 equiv) in one portion, and the reaction was monitored by TLC (50:50 CH_2Cl_2 :Hexanes). After 1 hour, the reaction was complete. The reaction mixture was diluted with water and Et_2O , and the layers were separated. The aqueous layer was extracted once with Et_2O , and the organic extracts were combined and washed successively with 20% $\text{Na}_2\text{S}_2\text{O}_3$ (aq.), water, and brine. The Et_2O layer was dried with MgSO_4 , filtered, and concentrated in vacuo to provide a solid. This solid was dissolved in minimal CH_2Cl_2 , and was purified by flash chromatography using 50:50 CH_2Cl_2 :Hexanes to obtain arene **253** as a tan solid (6.37 g, 90% yield). R_F = 0.20 (15:85 EtOAc :Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.63 (d, J = 3.7 Hz, 1H), 6.58 (d, J = 3.7 Hz, 1H), 6.52 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 155.8, 148.9, 138.3, 128.7, 119.4, 111.4, 94.2, 67.4, 57.5, 56.1, 25.6; IR (film) 2939, 2842, 1733, 1682, 1577, 1371, 1206, 1116, 1100 cm^{-1} ; HRMS (FAB) $^+$ calc'd for $[\text{C}_{12}\text{H}_{12}\text{NO}_3\text{I}]^+$: m/z 344.9862, found 344.9849.



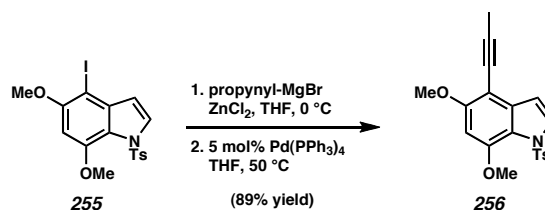
Indole 254. Indole **253** (5.97 g, 17.3 mmol, 1.00 equiv) was dissolved in THF (80.0 mL) at ambient temperature and stirred vigorously. At this stage, 10% NaOH (aq.) (80.0 mL) was added and the reaction stirred until complete consumption of indole **253** (ca. 1 hour).

The reaction mixture was diluted with water and EtOAc, and the layers were separated. The aqueous layer was washed once with EtOAc, and the organic extracts were combined and washed with water and brine, dried with MgSO_4 , filtered, and concentrated in vacuo to provide indole **254** as a light-yellow solid (5.20 g, 98% yield).³² $R_F = 0.25$ (20:80 EtOAc:Hexanes); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.4 (br, 1H), 7.28 (t, $J = 2.7$ Hz, 1H), 6.60 (s, 1H), 6.18 (dt, $J = 0.7, 2.2$ Hz, 1H), 3.97 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125, MHz, $\text{DMSO}-d_6$) δ 152.4, 146.9, 132.6, 125.9, 121.1, 104.4, 91.9, 65.7, 57.9, 55.7; IR (film) cm^{-1} ; HRMS (FAB⁺) calc'd for $[\text{C}_{10}\text{H}_{10}\text{O}_2\text{NI}]^+$: m/z 302.9756, found 302.9754.



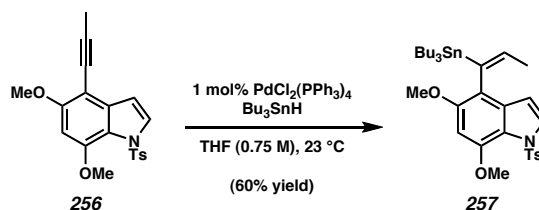
Arene 255. To a suspension of powdered KOH (4.95 g, 16.3 mmol, 1.15 equiv) and Bu_4NBr (788 mg, 2.45 mmol, 0.15 equiv) was added THF (125 mL), and the suspension was cooled to 0 °C. Indole **254** (4.95 g, 16.3 mmol, 1.00 equiv) was then added in one portion to the reaction mixture, and the solution was allowed to stir for 45 minutes at 0 °C. At this stage, TsCl (3.57 g, 18.8 mmol, 1.15 equiv) was added to the reaction mixture in a single portion, and the mixture was allowed to stir for an additional 10 minutes at 0 °C. The reaction mixture was then allowed to warm to ambient temperature and stir overnight. TLC analysis (35:65 CH_2Cl_2 :Hexanes) showed that minimal amounts of indole **254** remained, and thus, the reaction mixture was diluted with water and Et_2O . The layers were separated, and the aqueous layer was extracted 2x with Et_2O . The organic layers were combined and washed once with water and brine, dried with MgSO_4 , filtered, and concentrated in vacuo to yield a tan solid. This solid was dissolved in

minimal CHCl_3 , and purified by flash chromatography using 35:65 \rightarrow 75:25 CH_2Cl_2 :Hexanes to afford indole **255** as a white solid (5.51 g, 75% yield).³³ R_F = 0.30 (40:60 CH_2Cl_2 :Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, J = 3.9 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 3.7 Hz), 6.36 (s, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 148.2, 144.3, 137.7, 137.0, 129.8, 129.4, 127.3, 119.3, 110.5, 94.2, 67.1, 57.5, 55.8, 21.6; IR (film) 3148, 2939, 2845, 1578, 1463, 1352, 1255, 1213, 1171, 1134, 994 cm^{-1} ; HRMS (FAB⁺) calc'd for $[\text{C}_{17}\text{H}_{16}\text{O}_4\text{NS}]^+$: m/z 456.9845, found 456.9833.



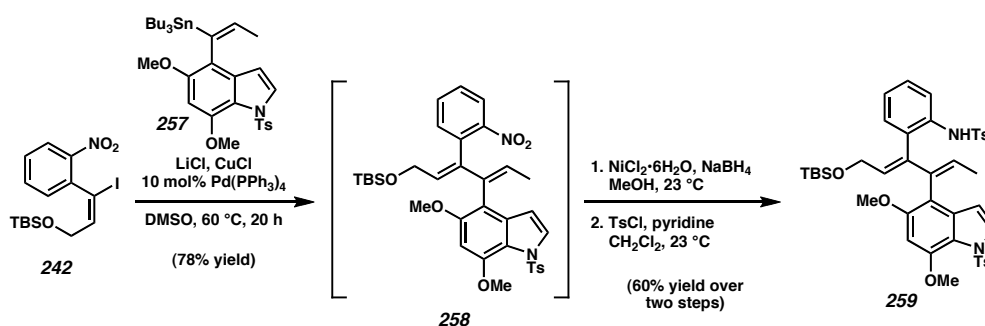
Alkyne 256. ZnCl_2 (2.84 mL of 0.5 M solution in THF, 1.42 mmol, 1.30 equiv) was added to THF (5.00 mL) at ambient temperature. The reaction mixture was then cooled to 0 $^\circ\text{C}$, and CH_3CCMgBr (2.84 mL of 0.5 M solution in THF, 1.42 mmol, 1.30 equiv) was added and a white precipitate formed. The suspension was stirred for an additional 30 minutes at 0 $^\circ\text{C}$. Indole **255** (500 mg, 1.09 mmol, 1.00 equiv) was charged into a separate round-bottom flask, followed by $\text{Pd(PPh}_3)_4$ (63.1 mg, 0.0545 mmol, 0.050 equiv) and THF (1.30 mL). This solution was then transferred via cannula to the white suspension at 0 $^\circ\text{C}$, and the resultant suspension was allowed to warm to ambient temperature over 10 minutes. The reaction mixture was then heated to 60 $^\circ\text{C}$ and monitored by TLC (30:70 EtOAc:Hexanes). After 40 minutes, the reaction was complete and allowed to cool to ambient temperature. The reaction mixture was diluted with water

and Et₂O, and the layers were then separated. The aqueous layer was washed 2x with Et₂O, and the Et₂O layers were combined and washed 2x with water, brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide a solid residue. This residue was recrystallized from EtOH to provide alkyne **256** as white flakes (357 mg, 89% yield). *R*_F = 0.40 (30:70 EtOAc:Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, *J* = 3.7 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 3.7 Hz, 1H), 6.30 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.6, 147.2, 144.2, 137.0, 136.1, 129.7, 129.3, 127.2, 119.0, 106.7, 96.9, 93.6, 91.6, 73.2, 56.9, 55.6, 21.5, 4.9; IR (film) 3153, 2940, 2847, 1595, 1490, 1360, 1262, 1209, 1172, 1130, 1107 cm⁻¹; HRMS (FAB⁺) calc'd for [C₂₀H₁₉O₄NS]⁺: *m/z* 369.1035, found 369.1033.



Vinyl Stannane 257. To a solution of alkyne **256** (650 mg, 1.76 mmol, 1.00 equiv) in THF (2.50 mL), PdCl₂(PPh₃)₂ (12.4 mg, 0.0176 mmol, 0.0100 equiv) was added and allowed to stir for 5 minutes at ambient temperature. At this stage, Bu₃SnH (595 μL, 2.20 mmol, 1.25 equiv) was added dropwise, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). After 6 hours, the reaction mixture was concentrated, and the crude oil underwent flash chromatography using 5:95 EtOAc:Hexanes to afford vinyl stannane **257** as a pale-yellow oil (700 mg, 60% yield). *R*_F = 0.45 (10:90 EtOAc:Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.72 (m, 3H), 7.25 (dd, *J* = 0.5, 8.5 Hz,

2H), 6.36 (m, 2H), 6.00 (q, $J = 6.4$ Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 2.40 (s, 3H), 1.56 (d, $J = 6.6$ Hz, 3H), 1.36 (m, 6H), 1.20 (hex, $J = 7.3$ Hz, 6H), 0.80 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.5, 145.3, 143.8, 139.8, 137.5, 137.3, 131.3, 129.2, 128.8, 127.2, 119.4, 117.7, 107.3, 94.4, 56.5, 56.0, 28.9, 27.3, 21.6, 17.0, 13.6, 10.2; IR (film) 2955, 2927, 2848, 1592, 1481, 1464, 1360, 1173, 1126 cm^{-1} ; HRMS (FAB^+) calc'd for $[\text{C}_{32}\text{H}_{46}\text{O}_4\text{NSSn}]^+$: m/z 660.2170, found 660.2198.



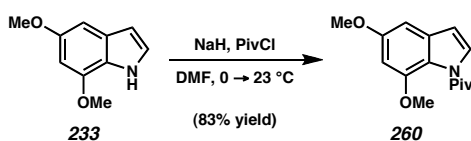
Diene 259. A Schlenk tube (20 mL) was charged with LiCl (118 mg, 2.78 mmol, 6.00 equiv) and flame-dried under vacuum. Upon cooling to ambient temperature, Pd(PPh)_4 (53.7 mg, 0.0464 mmol, 0.100 equiv) and CuCl (230 mg, 2.32 mmol, 5.00 equiv) were added, and the mixture was degassed 4x under vacuum with an Ar purge. DMSO (2.50 mL) was introduced with concomitant stirring, followed by a solution of arene **242** (195 mg, 0.464 mmol, 1.00 equiv) and vinyl stannane **257** (368 mg, 0.557 mmol, 1.20 equiv) in DMSO (800 μL , 400 μL rinse). The resulting mixture was rigorously degassed with Ar 4x by the freeze-pump-thaw process ($-78 \rightarrow 23$ °C, Ar). The reaction mixture was stirred for an additional 30 minutes at ambient temperature, then heated to 60 °C and followed by TLC (30:70 EtOAc:Hexanes). After 20 hours, the reaction was complete and allowed to cool to ambient temperature. The reaction mixture was diluted with Et_2O and washed with a 6:1 mixture of brine:5% NH_4OH (aq.). A precipitate forms in the

aqueous layer, and the two layers are separated. The aqueous layer was extracted 2x with Et₂O, and the Et₂O extracts are combined and filtered over a small pad of celite. The filtrate was then washed 2x with water and brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 25:75 EtOAc:Hexanes to provide diene **258** as a glue (240 mg, 78% yield). This material was used directly in the next reaction.

To a solution of diene **258** (220 mg, 0.332 mmol, 1.00 equiv) in MeOH (6.60 mL) at 0 °C was added NiCl₂•6H₂O (13.0 mg, 0.664 mmol, 2.00 equiv), and the reaction mixture was allowed to stir until the majority of the NiCl₂•6H₂O was dissolved. At this stage, NaBH₄ (50.2 mg, 1.33 mmol, 4.00 equiv) was added in several portions over 30 seconds, the reaction mixture was then allowed to warm to ambient temperature, and was monitored by TLC (30:70 EtOAc:Hexanes). After 90 minutes the reaction was complete and was quenched with water. The reaction mixture was diluted with Et₂O and the layers are separated. The aqueous layer was extracted 3x with Et₂O, and the organic extracts are combined, washed with water and brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide an aniline as a white glue (200 mg, 95% yield). This material was used directly in the next reaction.

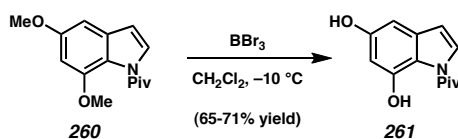
To a solution of the aniline (96.0 mg, 0.152 mmol, 1.00 equiv) in CH₂Cl₂ (3.00 mL) at ambient temperature was added pyridine (132 µL, 1.22 mmol, 8.00 equiv), and the reaction mixture was stirred for 10 minutes. TsCl (31.8 mg, 0.167 mmol, 1.10 equiv) was then added in one portion, and the reaction was followed by TLC (30:70 EtOAc:Hexanes). After 8 hours, the reaction color was orange-red and was complete.

The reaction mixture was concentrated in vacuo to provide a crude residue. To this residue was added heptane, and the volatiles were removed in vacuo (2x). The resulting residue was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide aniline **259** as a white foam (76 mg, 63% yield). $R_F = 0.30$ (30:70 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.78 (m, 4H), 7.68 (m, 3H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.27 (dt, $J = 1.7, 7.8$ Hz, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.04 (dt, $J = 1.0, 7.3$ Hz, 1H), 7.00 (dd, $J = 1.6, 7.4$ Hz, 1H), 6.57 (s, 1H), 6.32 (d, $J = 3.7$ Hz, 1H), 5.22 (t, $J = 6.4$ Hz, 1H), 5.12 (q, $J = 6.8$ Hz, 1H), 4.02 (s, 3H), 3.8 (s, 3H), 3.64 (dd, $J = 6.4, 13.7$ Hz, 1H), 3.50 (dd, $J = 6.4, 13.7$ Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H), 1.22 (d, $J = 6.8$ Hz, 3H), 0.77 (s, 9H), -0.18 (s, 3H), -0.19 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.2, 147.0, 144.1, 143.4, 137.7, 137.3, 136.5, 136.3, 135.1, 133.8, 131.3, 130.5, 129.6, 129.4, 129.0, 128.6, 127.7, 127.5, 127.4, 127.38, 123.1, 119.2, 117.6, 110.5, 106.4, 94.1, 60.8, 56.9, 55.8, 25.8, 21.6, 21.5, 18.1, 15.4, -5.2 , -5.3 ; IR (film) 3283, 2918, 2850, 1598, 1493, 1349, 1254, 1168, 1092 cm^{-1} ; HRMS (FAB $^+$) calc'd for $[\text{C}_{42}\text{H}_{50}\text{O}_7\text{Si}_2\text{N}_2]^+$: m/z 786.2829, found 786.2862.



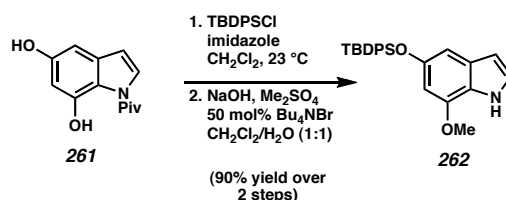
Indole 260. DMF (82 mL) was added to a round-bottom flask charged with NaH (1.33 g, 55.5 mmol, 3.00 equiv) at ambient temperature. The suspension was cooled to 0 °C and allowed to stir for 10 minutes. Subsequent dropwise addition of a solution of indole **233** (3.28 g, 18.5 mmol, 1.00 equiv) in DMF (8.00 mL, 4.00 mL rinse) to the NaH suspension resulted in bubbling. The reaction mixture was stirred for 20 minutes at 0 °C, PivCl (9.10 mL, 74.0 mmol, 4.00 equiv) was added, and the reaction mixture was allowed to slowly

warm to ambient temperature over 3 hours. After 3 additional hours of stirring, the reaction was complete by TLC (10:90 EtOAc:Hexanes). The reaction mixture was diluted with water and Et₂O, and the layers were separated. The aqueous layer was extracted 3x with Et₂O, and the organic extracts were combined and washed 3x with water, once with brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to afford indole **260** as a clear oil (4.03 g, 83% yield). R_F = 0.40 (20:80 EtOAc:Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, J = 3.4 Hz, 1H), 6.66 (d, J = 2.1 Hz, 1H), 6.49 (d, J = 3.4 Hz, 1H), 6.47 (d, J = 2.1 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 1.49 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 179.4, 157.0, 148.4, 131.7, 126.4, 121.7, 106.2, 96.6, 94.3, 55.8, 55.6, 42.5, 28.6; IR (film) 2968, 1719, 1612, 1592, 1478, 1287, 1204, 1174 cm⁻¹; HRMS (FAB⁺) calc'd for [C₁₅H₁₉NO₃]⁺: m/z 261.1365, found 261.1356.



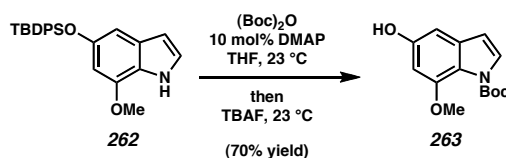
Bis Phenol 261. A solution of indole **260** (500 mg, 1.91 mmol, 1.00 equiv) in CH₂Cl₂ (38.0 mL) was cooled to –10 °C (super-saturated brine/ice bath), and stirred for 5 minutes. At this stage, BBr₃ (3.83 mL of a 1.0 M solution in CH₂Cl₂, 3.83 mmol, 2.00 equiv) was added dropwise over 2 minutes. The reaction was monitored by TLC (20:80 EtOAc:Hexanes), and was complete after ca. 25 minutes. The reaction mixture was quenched and diluted with water, and the solution was allowed to warm to ambient temperature. The layers were separated, and the aqueous layer was extracted 3x with EtOAc. The organic extracts were combined, washed with brine, dried with MgSO₄,

filtered, and concentrated in vacuo to provide a crude oil that was purified by flash chromatography using 10:90 EtOAc:Hexanes to provide indole **261** as a white solid (315 mg, 71% yield). $R_F = 0.45$ (30:70 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 11.17 (s, 1H), 7.64 (d, $J = 3.9$ Hz, 1H), 6.52 (d, $J = 3.9$ Hz, 1H), 6.46 (d, $J = 2.2$ Hz, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 4.81 (br, 1H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 178.9, 154.6, 146.5, 133.4, 126.7, 119.7, 110.9, 102.2, 97.5, 41.2, 29.1; IR (film) 3370, 2982, 2936, 1646, 1603, 1462, 1412, 1340, 1300, 1190 cm^{-1} ; HRMS (FAB $^+$) calc'd for $[\text{C}_{13}\text{H}_{15}\text{O}_3\text{N}]^+$: m/z 233.1052, found 233.1049.



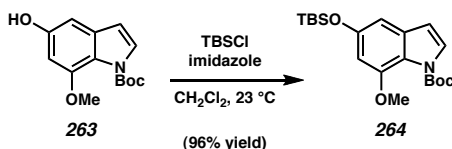
Arene 262. Indole **261** (1.43 g, 6.13 mmol, 1.00 equiv) and imidazole (920 mg, 13.5 mmol, 2.20 equiv) were dissolved in CH_2Cl_2 (61 mL) at ambient temperature. To this solution was added TBDPSCl (1.75 mL, 6.74 mmol, 1.10 equiv), and after 1–2 minutes a white precipitate formed. The reaction mixture was allowed to stir at ambient temperature for 6–12 hours, and monitored by TLC (20:80 EtOAc:Hexanes). Upon completion, the reaction mixture was quenched with water and then diluted with Et_2O . The layers were separated, the aqueous layer was washed 2x with Et_2O , and the organic extracts were combined and washed with brine, dried with MgSO_4 , filtered, and concentrated in vacuo to provide an oil that was used directly in the next reaction (2.83 g, 98% yield).

To a solution of the previous product (5.85 g, 12.4 mmol, 1.00 equiv) and Bu₄NBr (2.00 g, 6.20 mmol, 0.500 equiv) in CH₂Cl₂ (225 mL) at ambient temperature was added dimethyl sulfate (2.36 mL, 24.8 mmol, 2.00 equiv), and the reaction mixture was allowed to stir for several minutes. At this stage, a solution of NaOH (1.50 mg, 37.2 mmol, 3.00 equiv) in water (225 mL) was added, and the reaction mixture was stirred vigorously and monitored by TLC (20:80 EtOAc:Hexanes). After 3 hours, the reaction was complete, and the layers were separated. The aqueous layer was extracted once with CH₂Cl₂. The organic extracts were combined and washed with water, brine, dried with MgSO₄, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 7:93 EtOAc:Hexanes to provide indole **262** as a white foam (4.60 g, 92% yield, 90% yield over 2 steps). R_F = 0.40 (20:80 EtOAc:Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.06 (br, 1H), 7.78 (app. d, *J* = 6.8 Hz, 4H), 7.40 (m, 6H), 7.08 (s, 1H), 6.60 (s, 1H), 6.28 (s, 1H), 6.20 (s, 1H), 3.75 (s, 3H), 1.18 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 149.9, 145.7, 135.7, 133.7, 129.6, 128.4, 127.6, 123.8, 121.8, 102.6, 101.9, 97.5, 55.1, 26.7, 19.5; IR (film) 3436, 2958, 2932, 2858, 1586, 1478, 1428, 1313, 1151, 1114 cm⁻¹; HRMS (FAB⁺) calc'd for [C₂₅H₂₇O₂SiN]⁺: *m/z* 401.1811, found 401.1831.



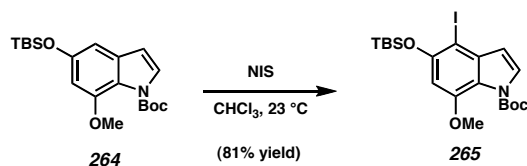
Phenol 263. To a solution of indole **262** (4.41 g, 11.0 mmol, 1.00 equiv) and DMAP (134 mg, 1.10 mmol, 0.100 equiv) in THF (110 mL) at ambient temperature was added (Boc)₂O (2.92 mL, 12.7 mmol, 1.15 equiv), and the reaction was monitored by TLC (20:80 EtOAc:Hexanes). Once complete (ca. 1 h), TBAF (12.1 mL from 1.0 M solution

in THF, 12.1 mmol, 1.10 equiv) was added to the reaction and monitored by TLC (20:80 EtOAc:Hexanes). The reaction was complete after 2–3 hours, and all the volatiles were removed in vacuo to provide an oil that was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide phenol **263** as a light-red oil (2.00 g, 70% yield over 2 steps). R_F = 0.35 (30:70 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 3.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 3.4 Hz, 1H), 5.02 (br, 1H), 3.90 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.6, 149.5, 148.9, 133.9, 129.2, 119.5, 106.7, 98.0, 97.0, 83.1, 55.8, 28.0; IR (film) 3428, 2980, 2935, 1727, 1596, 1369, 1345, 1303, 1258, 1145 cm^{-1} ; HRMS (FAB $^+$) calc'd for $[\text{C}_{14}\text{H}_{17}\text{O}_4\text{N}]^+$: m/z 263.1158, found 263.1167.



Indole 264. To a solution of phenol **263** (575 mg, 2.18 mmol, 1.00 equiv) and imidazole (327 mg, 4.80 mmol, 2.20 equiv) in CH_2Cl_2 (21.8 mL) at ambient temperature was added TBSCl (362 mg, 2.40 mmol, 1.10 equiv), and a white precipitate formed after 1 minute. The reaction mixture was allowed to stir and monitored by TLC (5:95 EtOAc:Hexanes). After 6 hours the reaction was complete. The reaction mixture was filtered through filter paper, washed with CH_2Cl_2 , and concentrated in vacuo to provide an oil that was purified by flash chromatography using 3:97 EtOAc:Hexanes to provide indole **264** as a clear oil (1.05 g, 96% yield). R_F = 0.40 (10:90 EtOAc:Hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 3.6 Hz, 1H), 6.60 (d, J = 2.0 Hz, 1H), 6.42 (d, J = 3.6 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 3.91 (s, 3H), 1.63 (s, 9H), 1.01 (s, 3H), 0.23 (s, 6H); ^{13}C NMR (125 MHz,

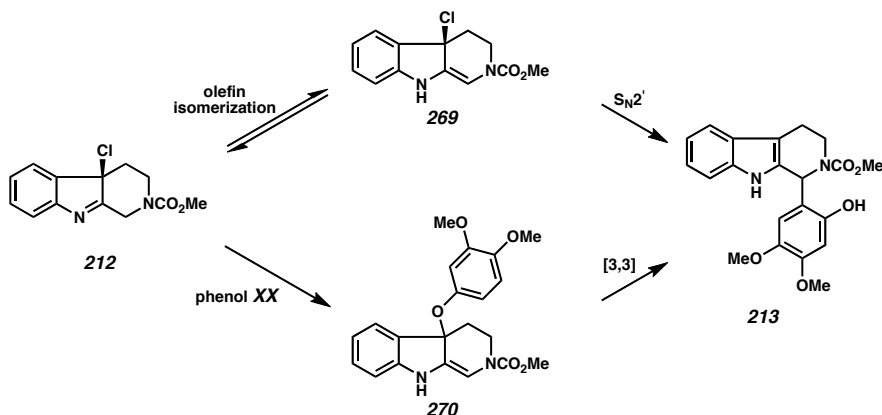
CDCl_3) δ 152.3, 149.5, 148.5, 133.7, 128.9, 120.0, 106.9, 103.1, 101.5, 82.9, 55.8, 28.0, 25.8, 18.2, -4.4; IR (film) 2956, 2931, 2858, 1728, 1586, 1473, 1368, 1294, 1150 cm^{-1} ; HRMS (FAB⁺) calc'd for $[\text{C}_{20}\text{H}_{31}\text{SiNO}_4]^+$: m/z 377.2022, found 377.2005.



Arene 265. To a solution of indole **264** (765 mg, 2.03 mmol, 1.00 equiv) in CHCl_3 (15.0 mL) at ambient temperature was added *N*-iodosuccinimide (477 mg, 2.13 mmol, 1.05 equiv) in one portion, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). The reaction mixture color changes upon the addition of NIS from colorless to wine-red over 30–60 minutes. The reaction was complete after 3 hours, and was quenched with H_2O (3.00 mL). To this mixture was added 5 drops of saturated $\text{Na}_2\text{S}_2\text{O}_3$ (aq.), and the mixture was allowed to stir for 20 minutes. At this stage, the layers were separated, the organic layer was diluted with Et_2O , washed once with brine, dried with MgSO_4 , filtered, concentrated in vacuo to provide a dark oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to provide arene **265** as a clear oil (830 mg, 81% yield). R_F = 0.40 (30:70 EtOAc:Hexanes); R_F = 0.40 (10:90 EtOAc:Hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.48 (d, J = 3.7 Hz, 1H), 6.58 (d, J = 3.7 Hz, 1H), 6.38 (s, 1H), 3.38 (s, 3H), 1.38 (s, 9H), 1.16 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.8, 149.8, 138.5, 129.8, 128.7, 120.6, 111.6, 101.0, 83.1, 71.9, 55.8, 28.1, 26.6, 19.0, -3.3; IR (film) 2957, 2931, 2858, 1732, 1574, 1469, 1360, 1292, 1271, 1209, 1158 cm^{-1} ; HRMS (FAB⁺) calc'd for $[\text{C}_{20}\text{H}_3\text{O}_4\text{NSi}]^+$: m/z 503.0989, found 503.1011.

3.9 Notes and References

- ¹ Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Gardner, D.; Willing, R. I. *Phytochemistry* **1999**, *51*, 153–157.
- ² Energy minimization calculations for Spartan were accomplished using AM1, equilibration geometry.
- ³ Chan, C.; Li, C.; Zhang, F.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 4839–4841.
- ⁴ The phenolic oxygen is bound to C(3) of the indole in the natural product, not C(2).
- ⁵ The mechanism for formation of phenol **213** has not been fully elucidated; however, Danishefsky proposes two possible mechanisms (ref. 3):



- ⁶ For the synthesis of racemic phalarine, see: Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1448–1550. For the asymmetric synthesis, see: Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 8506–8512.
- ⁷ Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1444–1447.
- ⁸ Gramine is 2-(*N,N*-dimethylaminomethylene)indole.

- ⁹ The synthesis of oxindole **214** required three additional steps starting from tetrahydro- β -carboline **203**. See: ref. 8 for synthetic details.
- ¹⁰ The mechanisms for the conversion of intermediates **224** and **225** to pentacycle **226** were shown in Schemes 3.2.1 and 3.2.2.
- ¹¹ For several examples of palladium(II)-catalyzed oxidative heterocyclizations onto styrenyl olefins, see: a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585. b) Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522–524. c) Trend, R.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788.
- ¹² For the synthesis of arene **234**, see: Kataoko, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566.
- ¹³ For the synthesis of vinyl stannane **236**, see: Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, *18*, 981–984.
- ¹⁴ For examples of phenol cyclizations, see: a) Larock, R. C.; Wei, L.; Hightower, T. *Synlett* **1998**, 522–524. b) For examples of alcohol cyclizations, see, Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749–7752. c) For examples of acid cyclizations, see: Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298–5300. d) For examples of tosylamide cyclizations, see: Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585, and references therein.
- ¹⁵ a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2892–2895. b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788.

- ¹⁶ Most cyclizations of this type using either Stoltz's conditions or DMSO/O₂ require >12 hours for acceptable conversion (>50%).
- ¹⁷ Liron, F.; Garrec, P. L.; Alami, M. *Synlett* **1999**, 246–248.
- ¹⁸ Liron, F.; Gervais, M.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2003**, *44*, 2789–2794.
- ¹⁹ Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731–5736.
- ²⁰ a) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740. b) Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267–2269.
- ²¹ Condie, G. C.; Channon, M. F.; Ivory, A. J.; Kumar, N.; Black, D. S. *Tetrahedron* **2005**, *61*, 4989–5004.
- ²² Slight modifications to the first two reaction conditions provided higher yields. See S.I. for reaction details.
- ²³ Henry, L. *Compt. Rend.* **1895**, *120*, 1265. For more recent examples, see: a) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884. b) Chung, W. K.; Chiu, P. *Synlett* **2005**, 55–58. c) Bernardi, L.; Bomini, B. F.; Capito, E.; Dessole, G.; Comes-Franchini, M.; Fochi, M.; Ricci, A. *J. Org. Chem.* **2004**, *69*, 8168–8171.
- ²⁴ Conditions screened include: BBr₃, BCl₃, TiCl₄, TMSI, and NaSEt with Δ.
- ²⁵ All other electron donating protecting groups, as well as a tosyl protecting group, led to C(2) or C(3) functionalization of indole **252**.
- ²⁶ Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.

- ²⁷ The formation of the sulfonamide was a surprisingly difficult reaction. The starting aniline and the product seemed to be sensitive to both acid and base, resulting in an unidentified impurity that made purification difficult.
- ²⁸ Although we were able to test the palladium(II)-catalyzed oxidative aniline cyclization, it appears that the aniline cyclized onto the wrong olefin. Even though it is not conclusive, there is no N-H stretch in the IR, and a HRMS of the products shows a mass corresponding to loss of H₂. Moreover, the ¹H NMR clearly shows which vinyl proton remains in the product.
- ²⁹ It should be noted that demethylation with one equivalent of BBr₃ cleanly afforded the C(7) mono-demethylated product. Although undesired for our studies, this selective transformation could prove valuable for the synthesis of other natural products or biologically active molecules.
- ³⁰ Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136.
- ³¹ a) When the reaction is run with 25 g of arene **251**, the yield for indole **233** is between 40–45%. b) The synthesis of indole **233** is also reported by Borchardt; however, several attempts using this procedure resulted in 30–40% yields of indole **233**, see: Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 3347–3349.
- ³² Indole **254** should be kept in a –20 °C freezer under Ar, away from light.
- ³³ Indole **255** can also be recrystallized from hot EtOH. However, prolonged heating to dissolve the final 5% of solid should be avoided, as decomposition and darkening of the solution occurs. Instead, once 95% of indole **255** has dissolved, perform a hot filtration and rinse, followed by cooling to effect crystallization and avoid decomposition.

